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10/772,964	02/04/2004	Claudia Mattern	85946.8276	5308

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EXAMINER

SASAN, ARADHANA

ART UNIT	PAPER NUMBER
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1615

MAIL DATE	DELIVERY MODE
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11/13/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/772,964

Applicant(s)

MATTERN, CLAUDIA

Examiner

Aradhana Sasan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 08/13/2007 are acknowledged.
2. Claims 1, 5, 8, 11, 12 and 14 were amended.
3. New claims 15-21 were added.
4. Claims 1-21 are included in the prosecution.

Response to Arguments

Rejection of claims 5, 8, 11, 12, and 14 under 35 USC § 112, second paragraph

5. In light of applicant's amendments, the rejection of claims 5, 8, 11, 12, and 14 under 35 USC § 112, second paragraph is withdrawn.

Rejection of claims 1-6, 8, and 13-14 under 35 USC § 103(a)

6. Applicant's arguments, see Page 6, filed 08/13/2007, with respect to the rejection of claims 1-6, 8, and 13-14 under 35 USC § 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) have been fully considered but are not persuasive.

Applicant argues that neither Illum nor Ko teach the use of high concentrations of lipophilic agents and that Illum teaches the use of as much as 10% phospholipids to enhance membrane permeability. Applicant states that Ko teaches the creation of an oil phase with roughly 45% of soybean oil and the claimed invention teaches a higher lipophilic concentration for a different reason.

However, Illum discloses a highly lipophilic composition. In the compositions for the gelatin microspheres and the chitosan microspheres, 90% of olive oil (100ml out of

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110ml total solution) and soybean oil (100ml out of 110ml total solution) was used respectively (Col. 7, lines 14-41). This percentage falls within the claimed range of 60% to 98% of lipophilic carrier of instant claim 1. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the drug delivery composition (with high lipophilic carrier or oil percentage) for the uptake of sex hormone drugs from the nasal cavity, as taught by Illum.

Ko is used as a secondary reference that provides the teaching of emulsion formulations of testosterone for nasal delivery.

In response to applicant's argument that the claimed invention carries at least 60% lipophilic carrier, which is intended to stabilize the suspension and maintain consistent serum levels upon administration, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Since all the claimed elements are found in Illum and Ko, one skilled in the art could have combined the elements and the combination would have yielded predictable results. See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 4/4/07 is maintained.

Rejection of claim 7 under 35 USC § 103(a)

7. Applicant's arguments, see Page 7, filed 08/13/2007, with respect to the rejection of claim 7 under 35 USC § 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) and further in view of Patel et al. (US 6,248,363) have been fully considered but are not persuasive.

Applicant argues that the examiner has failed to show how Patel remedies the deficiencies of Illum and Ko. With respect to claim 7, Patel provides the teaching of macroglycerides (as surfactants in formulations which improve the bioavailability of drugs), which is not expressly taught in the primary reference Illum.

Therefore, the rejection of 4/4/07 is maintained.

Rejection of claims 9-10 and 12 under 35 USC § 103(a)

8. Applicant's arguments, see Page 7, filed 08/13/2007, with respect to the rejection of claims 9-10 and 12 under 35 USC § 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) and further in view of Dondeti (International Journal of Pharmaceutics 1996) have been fully considered but are not persuasive.

Applicant argues that Dondeti teaches solid compositions, not liquids, and that Dondeti does nothing to remedy the deficiencies of Illum and Ko. Since the primary reference, Illum, and does not expressly teach viscosity modifying agents, Dondeti is used as a secondary reference to provide the teaching of viscosity modifying agents in formulations for nasal absorption of drugs. Dondeti teaches that: "drugs are usually administered to the nasal cavity in the form of solutions, suspensions, powders, microspheres, gels or inserts for local or systemic effect" (Page 119, right hand column).

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Therefore, one skilled in the art would find the teaching of viscosity modifying agents that are used for drug compositions (including solutions) that are administered in the nasal cavity obvious over the teaching provided by Dondeti.

Therefore, the rejection of 4/4/07 is maintained.

Rejection of claim 11 under 35 USC § 103(a)

9. Applicant's arguments, see Page 8, filed 08/13/2007, with respect to the rejection of claim 11 under 35 USC § 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) and further in view of Glass (US 5,897,894) have been fully considered but are not persuasive.

Applicant argues that the examiner has failed to show how Glass remedies the deficiencies of Illum and Ko and that the high lipophilic concentration is absent. This is not found persuasive because the high lipophilic concentration is present in the teaching provided by Illum. Glass provides the teaching of using silicon dioxide as a viscosity increasing or viscosity regulating agent. Since all the claimed elements are found in Illum, Ko, and Glass, one skilled in the art could have combined the elements and the combination would have yielded predictable results. See *KSR International Co. v. Teleflex Inc.*, 550 U.S. - , 82 USPQ2d 1385 (2007).

Therefore, the rejection of 4/4/07 is maintained.

MAINTAINED REJECTIONS:

The following is a list of maintained rejections:

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. Claims 1-6, 8, and 13-14, and new claims 15-17 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998).

Claims are drawn to a formulation for nasal application comprising a sexual hormone drug (testosterone), a lipophilic carrier (castor oil – a vegetable oil), a compound having surface tension decreasing activity (selected from surfactants), and a viscosity regulating agent (thickener or gelling agent).

Illum teaches a drug delivery system that enhances the uptake of active drug material from the nasal cavity (Col. 1, lines 16-19). The active drugs that can be used in this drug delivery system include sex hormones (Col. 9, line 31). Absorption enhancing materials such as surface active agents are also taught (Col. 5, lines 47-50). A preferred material is ... lysophosphatidylcholine produced from egg or soy lecithin (Col. 5, lines 38-39). Furthermore, "the drug to be administered to a mucosal surface in the ... nose could be administered as a viscous solution" (Col. 5, lines 6-8). The drug delivery system comprises microspheres. An emulsification technique using "purified olive oil" (Col. 6, line 48) and "soybean oil" (Col. 7, line 40) was used in the preparation of these microspheres. The microspheres are "made from materials that are known to swell in

contact with water to form a gel-like layer with good bioadhesive properties" (Col. 3, lines 5-7).

Illum does not specifically teach a drug delivery system comprising testosterone.

Ko et al. teach emulsion formulations of testosterone for nasal delivery (Abstract). The formulation materials include vegetable oil and surfactants (Page 198, Materials). The formulations are prepared by emulsification of the oil phase (containing the lipophilic testosterone and soybean oil) with the aqueous phase (further containing a surfactant) (Page 199, Preparation of formulations).

It would have been obvious to a person skilled in the art at the time the invention was made to combine the drug delivery system for nasal delivery teaching of Illum with the emulsion formulation of testosterone teaching of Ko to arrive at a nasal delivery system for testosterone. The motivation for combining these references is provided by Illum, which includes sex hormones as drugs that could be used in a nasal drug delivery system. For example, Illum teaches that progesterone "when given by the nasal route ... is absorbed effectively with a bioavailability similar to that for an intravenous injection..." (Col. 2, lines 12-13). Furthermore, since testosterone is a sex hormone that is lipophilic, the inclusion of oil to prepare an emulsion for enhancing the bioavailability of the testosterone and as a slow or sustained release agent would be obvious to a person skilled in the art.

Regarding instant claims 8 and 14, which disclose the weight percentage of component (c) and the sexual hormone drug, a person skilled in the art would modify the percentages of the formulation based on the required dosage and desired release profile, and the recited percentages are obvious variants unless there is evidence of criticality or unexpected results.

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) as applied to claims 1-6, 8, 13, and 14 above, and further in view of Patel et al. (US 6,248,363).

The teachings of Illum and Ko are stated above. The difference that Illum and Ko do not teach is the oleoyl macroglyceride as the surfactant.

Patel et al. teach that the bioavailability of drugs (like simvastatin) (Col 6, line 49) can be improved by their invention, which includes macroglycerides as the surfactant (Col 35, line 46, Col 65, lines 50-53, claim 16). Thus, a person skilled in the art would use a variety of macroglycerides for surfactants. These macroglycerides would include different fatty acid esters and oleoyl macroglyceride since it would be more compatible with humans. The motivation to use these surfactants would be to allow the emulsification and improve the bioavailability of poorly soluble, lipophilic drugs.

13. Claims 9-10, 12 and new claims 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998) as applied to claims 1-6, 8, 13, and 14 above, and further in view of Dondeti (International Journal of Pharmaceutics 1996).

The teachings of Illum and Ko are stated above. The difference not taught by Illum in view of Ko is the viscosity-regulating agent.

Dondeti teaches formulation parameters that affect nasal absorption of drugs. The use of HPMC (hydroxypropyl methylcellulose) (Page 118), methylcellulose (Page 118), and microcrystalline cellulose (Page 125) is taught.

Regarding instant claim 12, a person skilled in the art would modify the percentages of the formulation (specifically percentage of the viscosity regulating agent) in order to optimize the release profile and the recited percentage is an obvious variant unless there is evidence of criticality or unexpected results.

Therefore, it would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Illum and Ko (as stated above), and further use the viscosity modifying agents such as cellulose derivatives taught by Dondeti to arrive at the claimed invention. The motivation to combine these references is provided by Dondeti, who teaches, "increased viscosity prolongs the retention time of drug in the nasal cavity..."(Page 119).

14. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Illum (US 5,863,554), in view of Ko et al. (Journal of Microencapsulation 1998), and further in view of Glass (US 5,897,894).

The teachings of Illum and Ko are stated above. The difference not taught by Illum in view of Ko is colloidal silicon dioxide as the viscosity-regulating agent.

Glass teaches that "liquid oils can be thickened to increase their viscosity (e.g. with silicon dioxide) (Col. 5, lines 46-48). A person skilled in the art would use colloidal

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silicon dioxide, which is known in the art as a thickening agent, and would be an obvious choice of materials by the experimenter.

Conclusion

15. No claims are allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

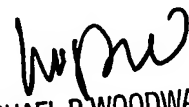
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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